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Original Article

Quantitative assessment of isolated rapid eye movement (REM) sleep without atonia without clinical REM sleep behavior disorder: clinical and research implications

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ABSTRACT

Background: Rapid eye movement (REM) sleep without atonia (RWA) is observed in some patients without a clinical history of REM sleep behavior disorder (RBD). It remains unknown whether these patients meet the refined quantitative electromyographic (EMG) criteria supporting a clinical RBD diagnosis. We quantitatively evaluated EMG activity and investigated its overnight distribution in patients with isolated qualitative RWA.
Methods: Fifty participants with an incidental polysomnographic finding of RWA (isolated qualitative RWA) were included. Tonic, phasic, and 'any' EMG activity during REM sleep on PSG were quantified retrospectively.
Results: Referring to the quantitative cut-off values for a polysomnographic diagnosis of RBD, 7/50 (14%) and 6/50 (12%) of the patients showed phasic and 'any' EMG activity in the mentalis muscle above the respective cut-off values. No patient was above the cut-off value for tonic EMG activity or phasic EMG activity in the anterior tibialis muscles. Patients with RWA above the cut-off value showed higher amounts of RWA during later REM sleep periods.
Conclusions: This is the first study showing that some subjects with incidental RWA meet the refined quantitative EMG criteria for a diagnosis of RBD. Future longitudinal studies must investigate whether this subgroup with isolated qualitative RWA is at an increased risk of developing fully expressed RBD and/or neurodegenerative disease.

1. Introduction

Rapid eye movement (REM) sleep [1] behavior disorder (RBD) is characterized by dream-enacting behaviors during REM sleep [2,3]. For the diagnosis of RBD, REM sleep without atonia (RWA) detected on electromyography (EMG) on nocturnal polysomnography (PSG) is mandatory according to the revised version of the International Classification of Sleep Disorders (ICSD-2) [4]. In contrast, RWA is observed incidentally on nocturnal polysomnography (PSG) in subjects with no history of RBD-like symptoms [5–8].

A correct diagnosis is important because RBD occurs not only idiopathically but also secondarily to α-synucleinopathies including Parkinson disease (PD) and dementia with Lewy bodies (DLB). It frequently represents a prodromal phase of these diseases [9–11]. Optimal cut-off values of RWA are extremely important for correct diagnosis. The ISCD-2 has not proposed quantitative cut-off values for RWA for a clear definition of RBD, but some previous researchers have examined this issue [6,12]. Montplaisir et al. suggested that 30% for tonic and 15% for phasic chin EMG activity are optimal cut-off values for the correct classification of RBD. The SINBAR (Sleep Innsbruck Barcelona) group has performed several studies of EMG activities in multiple muscles in RBD [13] and has presented normative values and an optimal cut-off in different types of EMG activity for diagnosis of RBD with the SINBAR method [12]. In that study, optimal cut-off values for a diagnosis of RBD were 18% for 'any' EMG activity in the mentalis muscle [12].

As described above, RWA is observed incidentally even without manifest RBD symptoms. However, it remains unclear whether a subgroup that is conventionally classified as isolated qualitative RWA can meet the refined quantitative EMG criteria for RBD.

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Considering the progression of RWA over time [14] and its association with behavioral manifestation of RBD [6] or with development to PD in RBD [15], RWA itself can be a precursor of RBD or reflect progressive pathologic process of RBD. However, this issue remains controversial. No report in the relevant literature to date has described the normal range or cut-off values for isolated qualitative RWA. In this study, we aimed at (i) assessing whether a subgroup of isolated qualitative RWA subjects fulfills quantitative RBD cut-off criteria and (ii) exploring specific characteristics of sleep pattern or overnight distribution of EMG activity in subjects with isolated qualitative RWA above quantitative RBD cut-off criteria to narrow candidates, who can face the highest risk of developing fully expressed RBD or neurodegenerative disease.

2. Methods

2.1. Patient selection

For the present study, all consecutive polysomnographic (PSG) reports that had been performed at the Sleep Laboratory of the Department of Neurology at Innsbruck Medical University between March 2003 and December 2005 were reviewed in order to identify the potential study candidates. In those years, the number of patients who underwent PSG for one or several nights ranged from 370 to 460. To identify the potential study candidates, all consecutive PSG reports of this time-period were screened for the qualitative description of RWA in the text. As potential study candidates were selected based on the qualitative description of RWA in the text, we cannot exclude that at least a small percentage of patients whose PSG reports did not refer to RWA in the text might have had a small amount of RWA when performing a quantitative assessment.

A total of 154 patients with a qualitative description of RWA in the PSG report were identified. REM sleep without atonia was defined as presence of an increased amount of phasic or tonic EMG activity in either the chin or extremity EMG channels [16]. Among this group, 50 patients were enrolled in this study based on the following inclusion and exclusion criteria. Inclusion criteria were an apnea–hypopnea index (AHI) <10/h (patients under effective treatment with nasal continuous positive airway pressure (n-CPAP) therapy were also included in the study). Exclusion criteria were the following: (i) AHI $\geq$ 10/h; (ii) presence of RBD and RBD-like symptoms confirmed by both the nocturnal video-PSG and a detailed face-to-face interview on sleep history at the time of the first contact with the patient and after visual identification of RWA; (iii) presence of any relevant psychiatric or neurological comorbidities; and (iv) use of medication acting on the central nervous system or potentially inducing RBD. The ethics committee of Innsbruck Medical University approved this analysis of retrospective data.

2.2. Nocturnal PSG

Using a digital polygraph (software version 4.00; Schwarzer Brainlab) with video monitoring of patient behavior, diagnostic n-PSG recordings and measurements were performed, including four channels of the scalp EEG (C3/A2, C4/A1, O1/A2, O2/A1), two electro-oculograms (EOG), mentalis electromyogram (EMG), electrocardiogram, nasal/oral airflow, an oximetry sensor for percutaneous oxygen saturation (SpO_2) recording, a microphone for snoring sounds, chest/abdominal respiratory effort, and anterior tibialis EMG for leg movements (bipolar derivations with two electrodes placed 3 cm apart on the belly of the anterior tibialis muscle of right and left legs). All PSG data recorded during 2003–2005 were rescored according to criteria set by the American Academy of Sleep Medicine (AASM) [17] with allowance to score slow wave sleep (SWS) activity in the central regions and to score REM sleep despite excessive EMG activity in the mentalis muscle [18]. The onset of REM sleep was determined by the occurrence of the first REM in the EOG channel, and the end of REM sleep was determined when either no REM was detected in three consecutive minutes or an awakening, K-complex, or spindles were observed.

2.3. Analysis of EMG activity

Tonic, phasic, and 'any' (either tonic or phasic) EMG activity was quantified manually in each muscle during REM sleep according to the methodology developed by the SINBAR group [12]. Artifacts in EMG channels were checked and excluded carefully before analysis of EMG activity. EMG activity in the mentalis muscle which occurred either before or during arousals related with any type of respiratory events were excluded from the analysis.

Tonic EMG activity was scored only in the mentalis muscle using full 30 s epochs of REM sleep. This activity was scored when the increased sustained EMG activity was present in >50% of the total 30 s epoch duration with amplitude of at least twice the background EMG muscle tone or >10 μV.

Phasic EMG activity was scored in 3 s mini-epochs in the mentalis muscle and anterior tibialis muscles. Each 3 s mini-epoch was scored as 'phasic' when a burst of EMG activity lasting between 0.1 and 5.0 s with amplitude exceeding twice the background EMG tone was observed, irrespective of its morphology.

We also scored each 3 s mini-epoch as having or not having 'any' EMG activity, irrespective of whether it contained tonic, phasic, or a combination of both kinds of EMG activities in the mentalis muscle. The rates of phasic and 'any' EMG activity were calculated as the number of 3 s mini-epochs with these EMG activities divided by the whole number of 3 s mini-epoch during REM sleep. The rate of tonic EMG activity was calculated as the number of 30 s epochs with this EMG activity divided by the whole number of 30 s epochs during REM sleep.

The periodic limb movements during sleep (PLMS) were scored during REM sleep and non-REM (NREM) sleep according to criteria set by the World Association of Sleep Medicine [17]. The PLMS during REM sleep were distinguished from phasic EMG activity by their characteristic periodicity and were excluded from quantitative analysis of RBD-related phasic EMG activity [12,13,19].

2.4. Statistical analysis

After checking the normality of distribution of the rates of each EMG activity for all patients, phasic EMG activity in the mentalis muscle and in the anterior tibialis muscles were compared using Kruskal–Wallis tests with a post hoc test using Steel–Dwass method for non-parametric data.

To investigate differences in demographic and polysomnographic variables, and distribution of each type of EMG activity during the night, the patients were divided into two groups: (i) RWA above the cut-off group having the percentage of phasic EMG activity in mentalis muscle higher than the optimal cut-off value for EMG activity (16.3%) [12], and (ii) RWA below cut-off group having a percentage lower than the cut-off value [12]. Demographic and polysomnographic variables, and amount of each type of EMG activity in total REM sleep are compared between the two groups using the Mann–Whitney *U*-test. For comparison of number of the subjects having AH $\geq$ 5/h between the two groups, χ^2-tests were conducted. To investigate distribution of each type of EMG activity, REM sleep was divided into four periods depending on its onset from sleep onset: first REM sleep (started within 2 h from sleep onset), second REM sleep (within 2–4 h), third REM sleep (within 4–6 h), and fourth REM sleep ($\geq$6 h after sleep onset). Two-way repeated measures analysis of variance was conducted for each type of EMG activity (group vs REM sleep episode temporal sequence).

If significant group × REM sleep episode temporal sequence interaction was found with this analysis, post hoc analysis was conducted using Friedman's analysis adjusted with Bonferroni's correction in each group. These statistical analyses were conducted using R version 2.15.1, or SPSS version 17.0J where possible.

3. Results

3.1. Demographic, clinical and PSG findings of subject patients

During 2003–2005, 50 patients were identified who met our inclusion criteria with an incidental finding of RWA. They were 40 men and 10 women with mean age of 49.3 ± 14.4 [18–73] years. The primary reasons for polysomnographic work-up were the following: suspected sleep-related breathing disorders ($n = 34$), suspected excessive daytime sleepiness ($n = 8$), insomnia ($n = 6$), circadian rhythm disorder ($n = 1$), and suspected sleep-related movement disorder ($n = 1$). Table 1 presents demographic and PSG variables of the patients. Motor activities other than RWA detected on n-PSG were the following: PLMS during NREM sleep (≥5/h) ($n = 29$), PLMS during REM sleep (≥5/h) ($n = 9$), fragmentary myoclonus ($n = 9$), neck myoclonus ($n = 2$), and alternative leg muscle activation ($n = 1$).

3.2. Quantitative assessment of EMG activity

In all, 74,579 mini-epochs (3 s) and 6309 full 30 s epochs of REM sleep were analyzed manually on each muscle recording in the 50 patients. The mean number of 3 s mini-epochs analyzed per patient was 1491.6 ± 370.8 (785–2425). The following artifacts were carefully checked for and excluded: snoring artifacts in the mentalis muscle, respiratory event-related motor activity, and recording artifacts in the mentalis muscle and in anterior tibialis muscles. In total, 1324 mini-epochs were excluded from calculation.

3.3. Distribution of the percentages of each type of EMG activity referring to the optimal cut-off values for the diagnosis of RBD

Fig. 1 presents the percentages of each type of EMG activities and subjects having EMG activity above the cut-off values for diagnosis of RBD. A significant difference was found between the percentages of phasic EMG activities in mentalis muscle, left tibialis muscle, and right tibialis muscle ($\chi^2 = 16.18$, df = 2, $P < 0.01$).

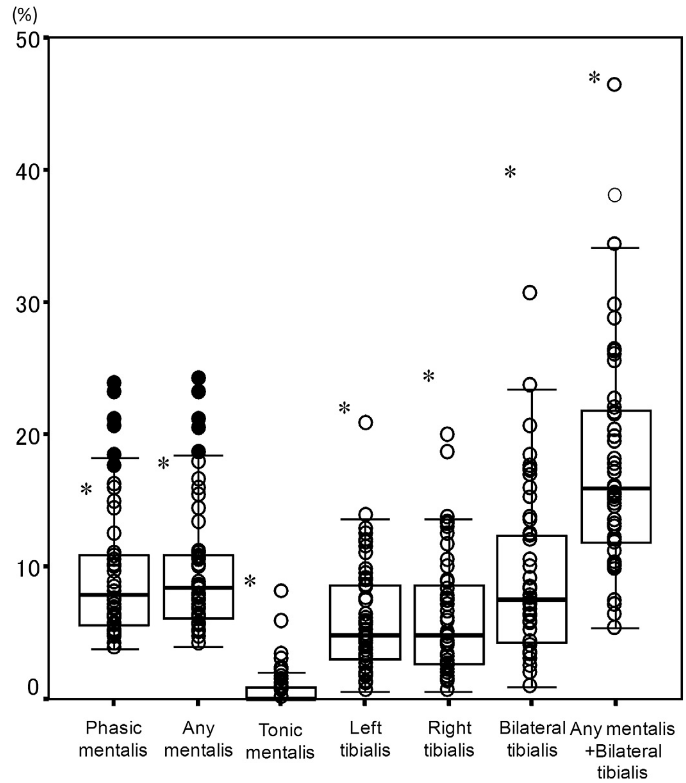

Fig. 1. Distribution of the percentages of each electromyographic (EMG) activity referred to the optimal cut-off values for rapid eye movement sleep behavior disorder (RBD) diagnosis. Asterisks denote the optimal cut-off values for diagnosis of RBD from our previous study. Filled circles represent patients having EMG activity above the cut-off. Open circles represent patients having EMG activity below the cut-off.

Phasic EMG activity was higher in the mentalis muscle than in either the left or right tibialis muscles ($P < 0.01$, respectively). Optimal cut-off values of muscle activities for a diagnosis of RBD supplied in our previous SINBAR study [12] are also shown as asterisks in Fig. 1. The cut-off values of all different EMG activities presented as asterisks were the following: 16.3% for phasic in mentalis, 18.2% for 'any' in mentalis, 9.6% for tonic in mentalis, 22.4% for phasic in left anterior tibialis, 24.8% for phasic in right anterior tibialis, 39.2% for phasic in bilateral anterior tibialis, and 46.4% for combination of 'any' in mentalis and phasic in bilateral anterior tibialis [12]. Seven out of 50 (14%) and six of 50 (12%) patients with isolated qualitative RWA showed higher phasic and 'any' EMG activity in the mentalis muscle than the cut-off values, respectively. All the seven subjects in the RWA above cut-off group were male, and six of these seven subjects (85.7%) were aged >40 years (Fig. 2). In contrast, no patient with isolated qualitative RWA showed EMG activity higher than the cut-off values for phasic EMG activity in bilateral anterior tibialis muscles, for combination of 'any' EMG activity in the mentalis and phasic EMG activity in bilateral anterior tibialis muscles, or for tonic EMG activity in mentalis.

Table 1
Demographic and polysomnographic characteristics of subjects ($n = 50$).

Sleep parameters	Values
Age (years)	49.3 ± 14.4 [18–73]
Sleep period time (min)	458.9 ± 23.7 [383.0–493.0]
Total sleep time (min)	409.8 ± 40.3 [297.0–460.0]
Sleep latency (min)	18.7 ± 15.3 [2.5–84.0]
REM latency (min)	85.4 ± 43.5 [9.5–202.0]
Sleep efficiency (%)	89.3 ± 7.2 [71.8–98.3]
WASO (%)	10.7 ± 7.2 [1.7–28.2]
Stage REM (%)	17.2 ± 4.3 [9.1–25.7]
Stage N1 (%)	12.6 ± 5.5 [5.4–37.1]
Stage N2 (%)	52.9 ± 8.5 [33–66.3]
Stage N3 (%)	6.4 ± 6.3 [0–18.1]
AHI (n/h)	3.6 ± 2.8 [0–9.8]
AHI ≥ 5/h (n (%))	15 (30.0)
Oxygen desaturation index (n/h)	1.1 ± 1.4 [0–5.0]
Mean SpO_2 (%)	93.8 ± 1.5 [90.3–96.9]
Minimal SpO_2 (%)	85.9 ± 5.2 [77.0–92.0]
PLMS index during NREM sleep (n/h)	21.7 ± 34.2 [0–175.0]
PLMS index during REM sleep (n/h)	2.3 ± 5.3 [0–27.0]

Values are expressed mean ± standard deviation [range].
RWA, REM sleep without atonia; WASO, wake after sleep onset; AHI, apnea hypopnea index; RDI, respiratory disturbance index; PLMS, periodic limb movement during sleep; NREM, non-rapid eye movement; REM, rapid eye movement.

3.4. Comparison of demographic and polysomnographic variables between the groups with phasic EMG activity in the mentalis muscle above and below the cut-off value for a diagnosis of RBD

The above cut-off group showed longer total sleep time (434.3 ± 38.8 (349.0–460.0) vs 405.8 ± 39.6 (297.0–456.0), $U = 70.0$, $P < 0.05$) and shorter sleep latency (8.5 ± 7.7 (2.5–25.0) vs 20.4 ± 15.6 (4.0–84.0), $U = 57.0$, $P < 0.01$). Neither age nor the other PSG variables showed differences between the two groups.

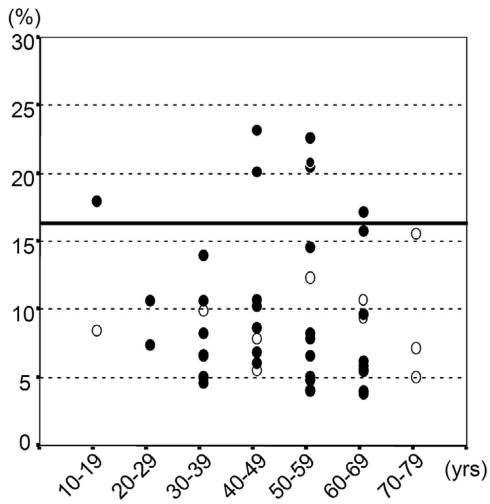

Fig. 2. Distribution of the percentage of phasic electromyographic (EMG) activity in the mentalis muscle over the different investigated age groups referred to the optimal cut-off value for rapid eye movement sleep behavior disorder (RBD) diagnosis. Filled circles represent male patients, open circles represent female patients. The bold line represents the optimal cut-off value of 16.3% for a diagnosis of RBD.

3.5. Distribution of EMG activities throughout a night

Table 2 presents group differences in the total amount and the distribution throughout one night of each type of EMG activity (phasic, tonic, and 'any' in mentalis muscle, phasic in bilateral tibialis, and combination of 'any' in mentalis and phasic in bilateral tibialis).

Interaction between the group and REM sleep episode temporal sequence was significant in phasic ($F(3, 84) = 4.290$), tonic ($F(3, 84) = 7.820$) and 'any' ($F(3, 84) = 4.468$) in mentalis, and combination of 'any' in mentalis and phasic in bilateral tibialis ($F(3, 84) = 3.155$) ($P < 0.05$, respectively). The main effects of REM sleep episode temporal sequence were also significant in phasic ($F(3, 84) = 8.708$), tonic ($F(3, 84) = 6.927$), and 'any' ($F(3, 84) = 8.205$) in mentalis, and combination of 'any' in mentalis and phasic in bilateral tibialis ($F(3, 84) = 8.506$) ($P < 0.01$, respectively). Post-hoc analysis revealed that in the RWA above cut-off group, phasic and 'any' in mentalis, and the combination of 'any' in mentalis and phasic in bilateral tibialis in the fourth REM sleep cycle were significantly higher than those in the first REM sleep cycle ($P < 0.05$, respectively). In the RWA below cut-off group, no significant difference in each type of EMG activity was found in the REM sleep episode temporal sequence.

In group comparison, the RWA above cut-off group showed higher amount of each type of EMG activity during a whole night compared to the below cut-off group; phasic in mentalis ($Z = -4.208$, $P < 0.01$), tonic in mentalis ($Z = -2.321$, $P < 0.05$), 'any' in mentalis ($Z = -4.208$, $P < 0.01$), and combination of 'any' in mentalis and phasic in tibialis ($Z = -3.900$, $P < 0.01$). In each REM sleep episode, the RWA above cut-off group showed higher phasic in mentalis, 'any' in mentalis and combination of 'any' in mentalis and phasic in bilateral tibialis compared to the RWA below cut-off group ($P < 0.01$, respectively). As for tonic in mentalis, the differences were observed only in the third and the fourth REM sleep cycle ($P < 0.05$, respectively).

4. Discussion

This is the first investigation into whether a subgroup of patients conventionally classified as RWA would meet the refined

Table 2
Distribution of the different EMG activity measures over the night.

EMG activity	REM sleep episode temporal sequence	Total subjects ($n = 50$)	Subjects above the cut-off ($n = 7$)	Subjects below the cut-off ($n = 43$)	P, interaction (group × REM sleep episode temporal sequence)	P
Phasic in mentalis	1	7.7 (5.2)	18.5 (1.7)	6.2 (3.8)	<0.05	<0.01
	2	9.0 (7.5)	17.6 (2.6)	7.2 (5.7)		<0.01
	3	1.0 (7.9)	21.4 (9.9)	8.5 (5.7)		<0.01
	4	2.4 (6.4)	25.2 (5.8)[a]	7.0 (5.8)		<0.01
	Total REM	9.6 (5.3)	20.9 (2.6)	6.9 (4.6)	–	<0.01
Tonic in mentalis	1	0.3 (0)	0 (0)	0 (0)	<0.05	NS
	2	0.9 (0)	0 (0)	0 (0)		NS
	3	1.2 (0)	2.0 (6.3)	0 (0)		<0.05
	4	1.1 (0.9)	1.8 (5.8)	0 (0)		<0.05
	Total REM	0.8 (0.8)	2.2 (2.7)	0 (0.7)	–	<0.05
'Any' in mentalis	1	7.9 (4.9)	18.7 (1.2)	6.3 (3.7)	<0.05	<0.01
	2	9.4 (7.7)	17.6 (2.6)	7.8 (7.3)		<0.01
	3	11.0 (7.9)	22.0 (9.6)	8.5 (5.7)		<0.01
	4	10.3 (7.1)	25.2 (7.4)[a]	6.9 (5.7)		<0.01
	Total REM	9.9 (5.0)	20.9 (2.7)	7.7 (4.5)	–	<0.01
Phasic in bilateral tibialis	1	7.0 (8.4)	5.5 (3.2)	4.2 (10.1)	NS	NS
	2	10.0 (10.8)	10.4 (6.7)	6.3 (11.3)		NS
	3	9.8 (9.0)	10.9 (4.6)	7.8 (8.4)		NS
	4	10.9 (10.3)	14.6 (4.8)	8.4 (10.0)		NS
	Total REM	9.3 (8.7)	12.1 (4.9)	7.1 (8.7)	–	NS
Combination of 'any' in mentalis and phasic in bilateral tibialis	1	14.2 (9.0)	22.4 (6.3)	10.9 (7.5)	<0.05	<0.01
	2	18.7 (10.0)	25.38 (1.8)	16.0 (8.6)		<0.01
	3	20.1 (9.5)	32.2 (13.4)	17.4 (7.8)		<0.01
	4	20.2 (11.6)	35.9 (7.6)[a]	17.8 (10.8)		<0.01
	Total REM	17.8 (10.2)	28.6 (5.3)	15.2 (8.1)	–	<0.01

EMG, electromyography; REM, rapid eye movement; NS, not significant.
Data are expressed as medians (interquartile ranges).
[a] $P < 0.05$ compared with first REM sleep episode.

quantitative EMG criteria for RBD. The answer to this question is extremely important in light of the fact that these cases might present the population at highest risk to develop fully expressed RBD or neurodegenerative disease. In this study, more than 10% of patients with isolated qualitative RWA met the quantitative criteria of phasic and 'any' EMG activity in mentalis muscle for RBD diagnosis.

4.1. EMG activity compared to optimal cut-off values for diagnosis of RBD

Referring to the optimal cut-off values for polysomnographic diagnosis of RBD from our previous study, as for 'phasic' EMG activity and 'any' EMG activity in mentalis muscle, 14% (7/50) and 12% (6/50) of patients with isolated qualitative RWA showed higher percentage of EMG activity than the cut-off values reported in our previous study [12]. In contrast, no patient with isolated qualitative RWA showed higher EMG activity than the cut-off values in phasic EMG activities in tibialis muscles and in tonic EMG activity in mentalis muscle. Montplaisir et al. first investigated the cut-off value of EMG activity for diagnosis of RBD [6]. In their study, $53.4 \pm 39.6\%$ for tonic EMG activity in mentalis muscle and $29.6 \pm 15.6\%$ for phasic EMG activity in mentalis muscle scored by 20 s epoch were observed in patients with RBD [6]. In our previous study using the SINBAR scoring method, the percentages of EMG activity were $51.8 \pm 32.8\%$ for tonic EMG activity in mentalis muscle, $40.9 \pm 19.0\%$ for phasic EMG activity in mentalis muscle and $66.5 \pm 25.2\%$ for 'any' EMG activity in mentalis muscle in patients with RBD [12]. Thus, tonic EMG activity in mentalis muscle in patients with symptomatic manifestation of RBD appeared to be much higher than that in the patients with isolated qualitative RWA. These results suggest that tonic EMG activity is more specific to RBD manifestation than phasic EMG activity in mentalis muscle consistent with the Montplaisir's study [6]. Moreover, either phasic EMG activities in limb muscles or tonic EMG activity in mentalis muscle can be more discriminative for clinical RBD. That is, muscle activity spread in distal limb muscle as well as sustained muscle activity is inferred to be specific to manifest RBD.

4.2. Distribution of each type of EMG activity

This study demonstrated that either levels or ranges of percentages of each EMG activity showed the following order: 'any' + phasic EMG activity in bilateral anterior tibialis > phasic or 'any' EMG activity in mentalis muscle > phasic EMG activities in anterior tibialis muscles > tonic EMG activity in mentalis muscle. In the mentalis muscle, patients with isolated qualitative RWA showed similar levels of phasic and 'any' EMG activity because patients with isolated qualitative RWA showed quite low tonic EMG activity. Comparison of phasic EMG activities among the mentalis muscle and anterior tibialis muscles showed that phasic EMG activity in mentalis muscle was higher than those in anterior tibialis muscles. The facts that EMG activity in relation to respiratory events was carefully excluded, and that none of the subjects with mild obstructive sleep apnea (OSA) exceeded the recently proposed cut-offs for a diagnosis of RBD, make us confident that the presence of OSA did not cause an overestimation of the proportion of patients having RWA above the cut-off. Abnormal sleep behaviors in RBD found in previous studies are likely to correspond to limb movements [20,21]. In addition, our previous study revealed that phasic EMG activity during REM sleep was more common in distal than in proximal limb muscles in patients with RBD [13]. Considering these facts, the continuity of the levels and ranges observed in each EMG activity indicates that the spatial spread of abnormal EMG activity related to continuous disease progresses from subclinical RBD to clinical RBD, in which abnormal EMG activity might start from cranial nerve-innervated muscle [13]. That is, the results indicate heterogeneity of the disease status of the disorder.

4.3. PLMS as a potential marker of developing clinical RBD

Patients with RBD are generally known to exhibit a higher PLMS index not only during NREM sleep but also during REM sleep [4,22–24]. In the present study, 20/50 (40%) of the patients with isolated qualitative RWA showed PLMS index during NREM sleep > 15/h; 29/50 (58%) of them showed an index of >5/h. Regarding PLMS during REM sleep, 2/50 (4%) of the patients with isolated qualitative RWA showed PLMS index during REM sleep >15/h, and 9/50 (18%) of them showed an index of >5/h. In our previous study, PLMS during REM sleep in patients with RBD were associated with the amount of RWA and duration of RBD morbidity [22]. Considering this, PLMS during REM sleep may be regarded as a potential marker of developing clinical RBD, even in patients with isolated qualitative RWA. In this study, however, no significant correlation was found between the PLMS index during REM sleep and the amount of RWA. The reason for this finding could be explained by the small number of patients with PLMS during REM sleep in the current study.

4.4. Is the amount of RWA associated with its distribution throughout the night?

This study revealed that patients with RWA above the cut-off value are likely to show higher amounts of each type of EMG activity during later REM sleep periods. This finding was not observed in the RWA below the cut-off group. RBD manifestations, especially violent–aggressive motor features, are more likely to occur during later REM sleep cycles rather than shortly after sleep onset [2,25] regardless of the duration of the REM sleep period [25]. Taking into account that RBD manifestation typically involves phasic EMG activity in limb muscles [19], the distribution of RWA throughout the night can be associated with the tendency of occurrence of RBD manifestation in patients with clinical RBD. Consequently, it can be speculated that patients with isolated qualitative RWA who showed EMG activity higher than the optimal cut-off value for diagnosis of RBD constitute a subgroup of patients who can be expected to develop RBD manifestation in the near future. Considering that phasic eye movements are related to RBD intensity [26–29], neural activation of the parieto-occipital visual cortex inducing dream imagery [30,31] or the scanning of the dream scene [32], future investigation of the correlation between REM and isolated qualitative RWA could further support this speculation. From another perspective, observing a certain level of EMG activity during the last REM sleep period can be important to avoid missing subclinical RBD.

4.5. Age and gender profile of the subjects with isolated qualitative RWA above the RBD cut-off values

This study provides an age and gender profile of the subjects with isolated qualitative RWA above the cut-off scores for a diagnosis of RBD. All the subjects in the RWA above cut-off group were men, and six out of these seven subjects were aged >40 years (Fig. 2). The similar demographic profile between RWA and RBD with an earlier age of manifestation in RWA, however, may be in favor of the hypothesis that RWA is a potential precursor of RBD.

4.6. Is there need for quantitative assessment of RWA?

Based on the results presented herein, a certain percentage of patients with isolated qualitative finding of RWA showed excessive EMG activity comparable to definite RBD. Moreover, these patients showed overnight increase in each type of EMG activity, which could be associated with tendency of occurrence of RBD

manifestation in patients with clinical RBD. For that reason, not only qualitative but also quantitative assessment might be necessary for a diagnosis of RBD. Investigating the relationship between the quantitatively assessed RWA and findings of neurodegenerative biomarkers as well as REM density, which is associated with RBD manifestation or dream imagery [26,29–32], might be important to clarify whether the isolated qualitative finding of RWA is a potential early marker of the transition to RBD or neurodegenerative disease. Simultaneously, it is necessary to set a cut-off value for distinguishing abnormal EMG activity from normal activity. To date, no optimal cut-off value for isolated qualitative RWA has been put forth to distinguish a subclinical RBD from a normal one. In this study, the group with isolated qualitative RWA above cut-off had later REM sleep period dominant EMG activity, which could be associated with the tendency of RBD behavioral manifestations in patients with clinical RBD to occur later in the night. A follow-up study, especially of those patients with isolated qualitative finding of RWA above optimal cut-off for diagnosis of manifest RBD including neurodegenerative marker assessment, is desired to elucidate a clinical meaning of isolated qualitative RWA. The subgroup showing isolated qualitative RWA above the cut-off for diagnosis of RBD is probably worth consideration as a precursor of manifest RBD development in further longitudinal studies.

Some potential limitations exist for this study. First, as RWA is an isolated PSG finding with no overt clinical symptoms, cut-off values for RWA cannot be determined from the present data, but deserve normative data from a healthy population sample. Moreover, follow-up investigations are necessary to clarify the association between the level of isolated RWA and the possibility of the development of manifest RBD, particularly addressing patients who show isolated qualitative RWA higher than the cut-off scores for a diagnosis of RBD. Second, as data were retrospectively analyzed, EMG recordings of the upper limbs were not available. These recordings, however, were reported to have higher discriminative power for clinical RBD [12,13]. Third, there is a possibility that phasic EMG activity in the tibialis muscles was underestimated as it is sometimes difficult to distinguish between 'true' PLMS and phasic EMG activity during REM sleep, although we tried very carefully to exclude only 'true' PLMS during REM sleep following the methodology of our previous publications [12,13,19]. Fourth, findings of the present study are derived from a single night of PSG. The influence of night-to-night variability could therefore not be taken into account. Fifth, there exists no inter-rater agreement on the qualitative presence of RWA as data were selected from existing routine PSG reports.

5. Conclusion

This report is the first to describe a study investigating quantitative characteristics of isolated qualitative RWA. Our data demonstrated that a portion of subjects with incidental RWA meet the refined quantitative EMG criteria for a diagnosis of RBD according to any or phasic EMG activity in the chin. Tonic EMG activity and phasic EMG activity in anterior tibialis muscle are inferred to be more specific to RBD manifestation than phasic EMG activity in the mentalis muscle. Future longitudinal studies must investigate whether this subgroup of subjects with RWA is at high risk of developing fully expressed RBD or neurodegenerative disease.

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Conflicts of interest

This was not an industry supported study. Dr. Frauscher has received support for speaking engagements from UCB. Dr. Poewe has received consultancy and lecture fees from AstraZeneca International plc, Teva, Novartis AG, GSK, Boehringer–Ingelheim Pharma GmbH, UCB, Orion Pharma, Merck, Serono Laboratories Inc., and Solvay–Abbot. Dr. Inoue has received consultancy and lecture fees from Hisamitsu, Philips Respironics, Takeda Pharmaceutical Co. Ltd., GSK, Astellas Pharma, Inc., Sanofi–Aventis, Yoshitomi, Otsuka Pharmaceutical Co. Ltd., and Eisai Co. Ltd. Dr. Högl has received honoraria for speaking, serving on advisory boards or consulting from UCB, Pfizer; Mundipharma, BI GSK and Respironics. The other authors have indicated no financial conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.02.010.

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